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The stem cell niche: a new target in medicine

Cosimo De Bari, Sarah Pringle, Costantino Pitzalis and Francesco Dell'Accio

Purpose of review

Stem cells have a critical role in tissue homeostasis and repair throughout life. Their fate between self-renewal and differentiation is regulated by stem cell intrinsic determinants and by signals from a specialized microenvironment, the stem cell niche. Here, we focus on recent progress in the anatomical and molecular characterization of mammalian stem cell niches.

Recent findings

The location of stem cell niches in adult life is well known for some tissues such as bone marrow, skin and gut. Physical interactions with niche cells, orientation of the cleavage plane during stem cell mitosis, and molecular cross talk at the niche sites with involvement of the Wnt, Notch and bone morphogenetic protein pathways control the balance between symmetric and asymmetric division of stem cells and related cell fate specification outcomes. A deregulation in the control of these events in excess or in defect could lead to either poor tissue homeostasis/repair or to tumor formation.

Summary

The vibrant interest in stem cell niches and their molecular regulation arises from the exciting potential to influence stem cell functions in modern medicine. In the near future, targeting stem cell niches could be a cell-free strategy to achieve tissue repair and to re-establish tissue homeostasis.

Keywords

bone, regenerative medicine, stem cell niche, stem cells, tissue engineering

Introduction

Stem cells persist in most tissues in adult life and are thought to contribute to tissue homeostasis and repair. On a single-cell basis, they have the capacity to self-renew (that is, to produce more stem cells) and to differentiate into mature cell lineages [1]. Stem cell self-renewal and differentiation appear to be regulated by stem cell intrinsic determinants as well as by signals from a specialized nurturing microenvironment called 'stem cell niche'. The niche provides molecular signals that participate in regulating stem cell activity to ensure tissue homeostasis and repair while preserving a constant pool of stem cells.

Pioneering studies on the gonadal niches in invertebrates [2–4] have inspired a great deal of science in mammalian systems with spectacular advance in our knowledge in the last few years. In this article, we review recent progress in the anatomical and molecular characterization of mammalian stem cell niches (Fig. 1).

The bone marrow hematopoietic stem cell niches

The bone marrow hematopoietic stem cells (HSCs) are the best-characterized adult stem cells and have been purified to clinical grade close to homogeneity. Yet, only recently, several studies have shed light on their niche(s). Primitive HSCs are located close to the endosteal surface of trabecular bone and a subset of endosteal osteoblasts provide niche signaling [5,6]. The role of osteoblasts in regulating HSC number has been demonstrated by studies showing that mutant mice with expanded trabecular bone and increased numbers of osteoblasts exhibit concomitant proportionate increases in marrow HSCs without changes in committed progenitor populations [5,6]. Conversely, conditional ablation of osteoblasts in mice results in a reversible decrease in the number of marrow HSCs [7], indicating that osteoblasts are required for the maintenance of marrow HSCs. A possible mechanism by which osteoblasts regulate the number of HSCs is through secretion of osteopontin, a bone matrix glycoprotein that appears to maintain HSC quiescence and to negatively regulate HSC proliferation and activity [8*,9*].

The molecular cross talk at the interface between the niche osteoblasts and the adjacent HSCs is now a key area of investigation due to its therapeutic potential to control bone marrow HSCs. A complex paracrine signaling network is emerging. Kit ligand is expressed by osteoblasts

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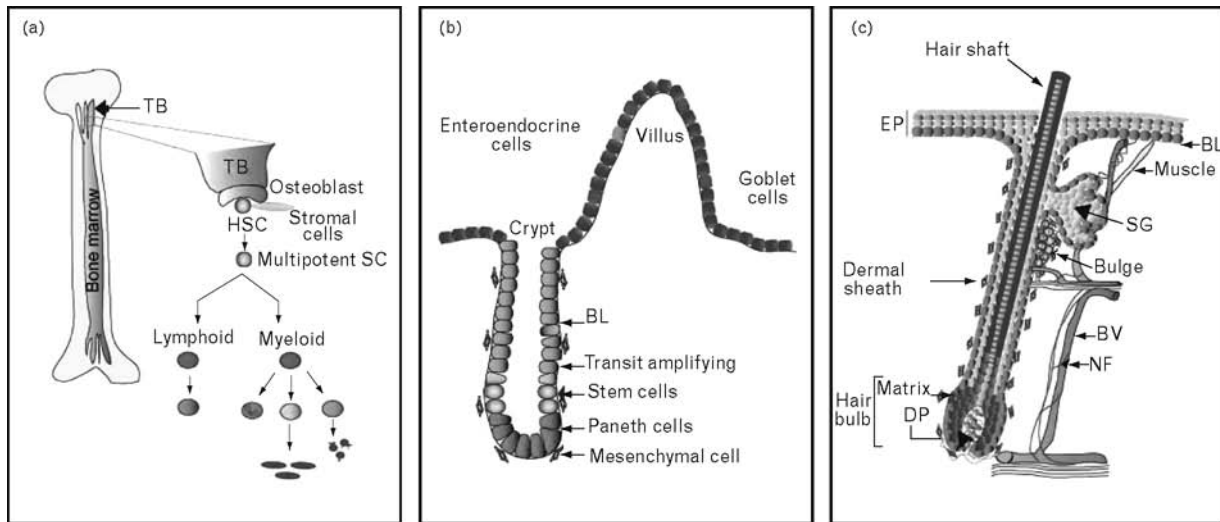
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Abbreviations

| | |
|--------------|----------------------------|
| BMP | bone morphogenetic protein |
| GLP-2 | glucagon-like peptide 2 |
| HFSC | hair follicle stem cell |
| HSC | hematopoietic stem cell |
| ISC | intestinal stem cell |
| MSC | mesenchymal stem cell |

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Figure 1 Stem cell niches

Three different stem cell niches are shown. (a) The endosteal niche of hematopoietic stem cells (HSCs) in the bone marrow. HSCs are located close to the endosteal surface of trabecular bone (TB) and a subset of endosteal osteoblasts are part of the niche. When the contact between osteoblasts and HSCs is lost, HSCs activate and differentiate towards blood lineages. (b) In the small intestine, stem cells reside near the base of each crypt, depicted here as a tube of cells. Intestinal stem cells give rise to four different progeny: Paneth cells, enteroendocrine cells, goblet cells, and absorptive enterocytes. The crypt epithelium is separated by a basal lamina (BL) that is surrounded externally by mesenchyme. The mesenchymal cells emit signals that participate in regulating stem cell activity. (c) In the skin, hair follicle stem cells reside in the 'bulge' region, located below the sebaceous gland (SG) and at the juncture of the erector pili muscle. The follicle is surrounded by a basement lamina (BL), which in turn is surrounded by a dermal sheath. Bulge stem cells give rise to transit-amplifying matrix cells, which proliferate and then differentiate to produce the hair shaft and the channel that surrounds it. Matrix cells are surrounded by a pocket of specialized mesenchymal cells, the derma papilla (DP). Nerve fibers (NFs) innervate the epidermis (Ep) and the bulge, and blood vessels (BVs) provide nutrients. Adapted from Fuchs *et al.* [1].

and is able to activate Kit on the cell surface of HSCs [10]. The Notch ligand Jagged1 is also expressed by osteoblasts while Notch1 is activated in HSCs, thus suggesting the involvement of the Notch signaling pathway in the modulation of HSCs by osteoblasts [6]. Indeed, there is evidence that Notch signaling would repress differentiation programs in HSCs thereby facilitating HSC competence to Wnt-induced proliferation [11*,12]. Another important interaction is between the ligand angiopoietin-1 at the osteoblast surface with the receptor Tie-2 expressed on HSCs, shown to modulate HSC quiescence and adhesion to the endosteal niche via N-cadherin expression [13].

The cross talk at the niche could contribute to regulating expression and activity of mediators of HSC quiescence/self-renewal such as bmi-1 [14], p21 [15], p18 [16], and the Ets transcription factor MEF/ELF4 [17*], or lead to inhibition of glycogen synthase kinase-3 (GSK-3), recently shown to maintain HSCs while expanding the progenitor pool [18**].

Intriguingly, HSCs express a calcium-sensing receptor that gives them the ability to sense and respond to calcium concentrations. HSCs lacking this receptor show decreased homing to the endosteal niche, suggesting a role of bone mineral gradients in the lodgment and

retention of HSCs [19**]. An unanticipated player in the process of signal integration within the niche is the sympathetic nervous system, which appears to regulate the attraction of HSCs to their niche [20**]. Adrenergic signals control granulocyte colony-stimulating factor (G-CSF)-induced osteoblast suppression and bone CXCL12 downregulation, leading to HSC egress into the circulation [20**]. CXCL12 is indeed highly expressed in bone tissues and is believed to be critical for the attraction and retention of HSCs to their niches [21].

The recent finding that CD150 expressing HSCs are more abundant in the perivascular area of sinusoids than at the endosteal site [22**] points to the perivascular area being a potential niche site for HSCs within the bone marrow. Indeed, marrow sinusoidal endothelial cells express cytokines such as CXCL12 and adhesion molecules such as E-selectin and vascular cell adhesion molecule 1 that are important for HSC mobilization, homing and engraftment [23*,24]. Since the fenestrated sinusoidal endothelium allows flow of blood-borne factors across its wall, the association of HSCs with sinusoids would ensure maintaining homeostatic blood cell production and enabling prompt responses to hematological stresses. Studies are now awaited to investigate whether the perivascular and endosteal sites represent distinctive specialized niches for different HSC subsets or if the

perivascular area is simply a stopover for HSCs en route to circulation.

The small intestinal stem cell niche

Multipotent intestinal stem cells (ISCs) reside in a ring about four cell diameters from the bottom of the crypt of Lieberkühn, a finger-like invagination of the epithelium into the underlying mesenchyme at the base of the villus in the small intestine, and differentiate to give rise to the absorptive enterocytes and to three types of secretory cells: goblet, enteroendocrine, and Paneth cells. While Paneth cells complete their differentiation at the crypt base, the other three epithelial lineages migrate from the crypt towards the tips of adjacent villi and differentiate. Asymmetric cell division of ISCs, proliferation of transit-amplifying cell progenies, distinct migratory patterns, specific differentiation programs, and correct positional information are all necessary for the rapid homeostatic renewal of the villus structure [25]. The mesenchyme surrounding the epithelial crypt is thought to be a main source of signals mediating different cell fates along the crypt axis. The canonical Wnt pathway plays a key role in the maintenance of ISCs and in the modulation of their activity and is able to induce cell-type-specific gene expression programs [26,27]. A Wnt gradient is suggested by the distribution of nuclear versus cytoplasmic β -catenin along the epithelium of crypts and villi [25]. Canonical Wnt signaling also ensures proper cell positioning in the intestinal epithelium through the EphB/ephrinB system [28]. Genetic studies also implicate Notch signaling in the maintenance of ISCs and in ensuring proper cell-fate specifications in the transit-amplifying cell compartment [29^{••},30^{••}]. Thus, ISCs are regulated by Wnt and Notch signaling according to combinatorial rules that are similar to those that operate in the bone marrow for the regulation of HSCs.

The bone morphogenetic protein (BMP) signaling pathway functions as a negative regulator of ISC proliferation. Conditional deletion of the BMP receptor type IA in epithelial cells results in expansion of the ISC population [31]. Inhibition of BMP signaling by transgenic overexpression of the BMP inhibitor Noggin leads to the formation of numerous ectopic crypt-like structures [32].

Another player in the regulation of crypt cell activity is glucagon-like peptide 2 (GLP-2). GLP-2 is produced by enteroendocrine cells, which sense the nutrient environment in the gut lumen, and stimulates production of enterocytes, which conversely absorb nutrients [33]. Intriguingly, the GLP-2 receptor is expressed not in the crypt epithelium but in a subset of enteric neurons, which therefore are postulated to fulfil a messenger role between the GLP-2 signal and the epithelial target cells [34]. Thus, as in the HSC endosteal niche, the nervous

system, which has the ability to integrate information throughout the organism, may modulate stem cell niche functions in the gut.

The hair follicle stem cell niche

In the skin there are two types of stem cells. The stem cell in the basal layer of the epidermis is responsible for the renewal of the stratified epidermis, while the hair follicle stem cell (HFSC), which resides in the 'bulge' region located below the sebaceous gland and at the juncture of the erector pili muscle, is responsible for the regeneration of hair and sebaceous glands [35]. Initially, it was thought that bulge stem cells were also providing homeostatic replenishment to the epidermis. Recent evidence, however, indicates that bulge HFSCs are not required for physiological epidermal homeostasis, although during wound healing they can contribute to epidermal regeneration and repair [36^{••},37^{••}]. Thus, epidermal basal cells and bulge HFSCs appear to be distinct stem cell populations.

In the early 1990s it was discovered that label-retaining, quiescent cells are located in the bulge region [38], but only recently mouse transgenic strategies have allowed prospective isolation of viable HFSC populations for functional analysis and genetic profiling [39–42]. As in the ISC niche, the Wnt signaling pathway plays a crucial role in the hair follicle system, affecting all phases of stem cell activity, from quiescence to proliferation, fate determination and terminal differentiation [43].

Using tissue-specific and inducible loss-of-function strategies in mice it has been shown that ablation of Notch1 during embryonic development does not perturb formation and patterning of hair follicle placodes, while postnatal inactivation of Notch1 results in almost complete hair loss, thus indicating that Notch1 is essential for postnatal hair follicle development and homeostasis [44[•]].

BMP signaling is also essential, as conditional ablation of the BMP receptor IA results in hair follicle defects [45]. Mice lacking the BMP inhibitor Noggin show defects in the function of the canonical Wnt pathway in the hair follicle [46], suggesting cross talk between the BMP and the Wnt signaling pathways.

Telomere shortening impairs hair growth by inhibiting mobilization of stem cells out of their niche. In contrast, conditional overexpression in mouse skin epithelium of the catalytic component of telomerase Tert causes proliferation of HFSCs in the bulge, thereby facilitating robust hair growth through an unconventional mechanism that does not involve the synthesis of telomere repeats [47[•],48[•]]. Conditional deletion of Rac1, a negative regulator of c-Myc, in the adult mouse epidermis

stimulates proliferation and terminal differentiation of HFSCs and interfollicular stem cells [49]. Studies are now awaited to allocate these molecules within the intricate puzzle of the signaling pathways that play a role in the modulation of stem cell function in the skin.

The mesenchymal stem cell niches

Mesenchymal stem cells (MSCs), conventionally derived from bone marrow, have the ability to self-renew and to differentiate into cartilage, bone and adipose tissue at the single cell level [50]. Their clinical use in orthopedic applications has been long sought and successfully achieved for cartilage and bone repair [51]. The lack of specific cell-surface markers has so far hindered the direct purification of a highly homogeneous population of MSCs, which would be desirable to obtain clinical grade, identity-characterized 'MSC products' with consistent and reproducible efficacy [51]. A reasonable enrichment of bone marrow MSCs prior to cell culture has been obtained using combinations of markers [52,53]. Multipotent MSCs have also been isolated from other tissues including periosteum, synovial membrane and synovial fluid [54–57]. Nonetheless, our knowledge on the MSC niches within their native tissues is very poor and whether MSCs are a cell culture artifact is a fundamental unresolved issue. It has been suggested that MSCs harbor in perivascular areas in the bone marrow [58], where they may be in close proximity to HSCs. The inhibitory effect of MSCs on cell proliferation *in vitro* [59] raises the attractive possibility of a role of MSCs in the maintenance of HSC quiescence. Intriguingly, following intramedullary transplantation into the bone marrow of immunodeficient mice, human MSCs differentiated into pericytes, stromal cells, bone-lining osteoblasts, and endothelial cells, all functional components of the marrow hematopoietic microenvironment [60••].

In the adult articular cartilage the superficial layer may function as a niche as it contains highly clonogenic multipotent cells that express Notch1 [61]. Compelling evidence is awaited, however.

Niches and stem cell divisions

Under homeostatic conditions stem cells self-renew and produce differentiated progeny. An individual stem cell can give rise to two identical daughter cells (symmetric division) or to two nonidentical daughter cells, one maintaining the stem-cell identity and the other becoming a differentiated cell (asymmetric division). The orientation of the cleavage plane during stem cell mitosis appears to have a crucial role in determining symmetric or asymmetric division, as demonstrated in invertebrate model systems [3,62,63]. When the stem cell divides with a cleavage plane perpendicular to the niche cell, both daughter cells remain in contact with the niche cell; in contrast, when the stem cell divides with a cleavage plane

parallel to the niche cell, then only one daughter cell remains in contact with the niche cell while the other is displaced away from the niche to relocate into a differentiation-promoting microenvironment [3,62,63]. In asymmetric cell division, an unequal segregation of specific cell-fate determinants between the two daughter cells has been well documented in invertebrate animals [64,65••,66]. Evidence for asymmetric cell division in mammalian stem cell systems has recently been provided for the basal cells of the skin epidermis [67••].

Stem cell niches and cancer

Niche structures appear to have the potential to enforce stem cell-like characteristics on nonstem cell types. Studies in invertebrates have shown that nonstem cell types may engage a vacant niche, reverting to a stem cell-like state [68,69]. The same could hold true in mammals, since in mice melanocyte stem-cell progeny migrates out of the niche, amplifies outside the niche and can then repopulate vacant niches, eventually returning to the quiescent state of stem cells [70]. Thus, there is the theoretical possibility that niches may be capable of contributing to abnormal tissue regulation, encouraging malignant cells by providing stem-like features to a more mature cell type. On the other hand, tumor cells appear to have the ability to establish favorable niches for metastasis [71••].

Niches prevent stem cell expansion [5,6]. Unregulated expansion of self-renewing stem cells could lead to tumor formation. Indeed, a subset of cancer cells within tumors, named cancer stem cells, may drive the growth and metastasis of these tumors [72]. The presence of a stem cell population in a tumor has clinical implications, as cancer stem cells would become the target for diagnosis and treatment. Recent studies indicate that compromised inheritance of cell-fate determinants contributes to unrestrained growth of the mutant neuroblast lineage in *Drosophila* via upregulation of specific target genes that control cell cycle, suggesting a mechanism by which loss of polarity in stem cells may lead to tumorigenesis [65••,73,74•]. Thus, correct regulation of stem-cell self-renewal requires a tight control of the re-distribution of cell-fate determinants between the two daughter cells during mitosis.

Conclusion

Advancement in our knowledge of the stem cell niches nourishes hopes of niche manipulations for therapeutic purposes to modify stem cell outcomes clinically. Thus, considerable attention is now directed to the niche cells and to their molecular signals to control stem cells. Molecular analyses of purified niche cells to determine their signaling repertoire have just started [75••]. These studies will help depict a comprehensive picture of the niche-orchestrated biological functions by understanding how

signals in the niches are coupled to events such as cell-cycle regulation and distinct transcriptional programs. In addition, they will allow the development of in-vitro systems that reproduce the in-vivo niches. The establishment of validated 'in-vitro niches' will enable systematic analyses of the molecular and cellular interactions at the niche sites as well as high throughput screenings of compounds affecting niche biology and outcomes. This will help investigate how niches are altered in situations of stress or pathology, such as cancer. The elucidation of the niche biology in health and disease has thus become a pressing issue in basic science and medicine. Such knowledge could lead to changes in established clinical measures; for instance, agents developed to target osteoblasts for bone disorders such as osteoporosis will have to be reassessed for their effects on HSC physiology. It will also instruct the development of novel therapies. The growing availability of small compounds to target signaling pathways even in a tissue/cell-specific fashion as well as of controlled delivery systems makes the molecular manipulation of the stem cell niche an attractive alternative to stem cell therapy to achieve tissue repair and re-establish tissue homeostasis. This would circumvent current limitations of the stem cell-based protocols associated with in-vitro cell-culture expansion, such as genetic and phenotypic instability, disease transmission, high costs, and variability [51].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 469–470).

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